Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Neophyr 225 ppm mol/mol, medicinal gas, compressed

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Nitric oxide 225ppm mol/mol.

Nitric oxide (NO) 0.225 ml in
Nitrogen (N_2) 999.775 ml.

A 10-liter gas cylinder filled to 150 bar supplies 1500 lof gas at a pressure of 1 bar at 15°C.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Medicinal gas, compressed.
Colourless and odourless gas.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Neophyr, in conjunction with ventilatory support and other appropriate active substances, is indicated:
for the treatment of newborn infants ≥ 34 weeks gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, in order to improve oxygenation and to reduce the need for extracorporeal membrane oxygenation.

as part of the treatment of perioperative pulmonary hypertension in adults and newborn infants, infants and toddlers, children and adolescents, ages 0-17 years in conjunction to heart surgery, in order to selectively decrease pulmonary arterial pressure and improve right ventricular function and oxygenation.

4.2 Posology and method of administration

Persistent Pulmonary Hypertension in the Newborn (PPHN)
Prescription of nitric oxide should be supervised by a physician experienced in neonatal intensive care.
Prescription should be limited to those neonatal units that have received adequate training in the use of a nitric oxide delivery system. Neophyr should only be delivered according to a neonatologist's prescription.

Neophyr should be used in ventilated newborn infants expected to require support >24 hours. Neophyr should be used only after respiratory support has been optimised. This includes optimising tidal volume/pressures and lung recruitment (surfactant, high frequency ventilation, and positive end expiratory pressure).

Pulmonary hypertension associated with heart surgery
Prescription of nitric oxide should be supervised by a physician experienced in cardiothoracic anaesthesia & intensive care. Prescription should be limited to those cardio-thoracic units that have received adequate training in the use of a nitric oxide delivery system. Neophyr should only be delivered according to an anaesthetist's or intensive care physician's prescription.

Posology

The posology will be determined in accordance with the medical condition of the patient.
Due to the potential risk of NO2 formation, continuous monitoring of NO2 must be performed.

Persistent Pulmonary Hypertension in the Newborn (PPH)
Newborns ≥ 34 weeks gestation: The maximum recommended dose of Neophyr is 20 ppm and this dose should not be exceeded. Starting as soon as possible, and in the first 4-24 hours of therapy, the dosage must be reduced gradually to 5 ppm or less, titrating it to the needs of the individual patient, as long as the clinical parameters (oxygenation, arterial pulmonary pressure) are within the desired limits. Inhaled nitric oxide therapy must be maintained at 5 ppm until an improvement in the oxygenation is observed in the newborn in such as way that the fraction of inhaled oxygen is diminished to below 60% (FiO_2 < 0.60).

The treatment can be pursued up to 96 hours or until the oxygen de-saturation is resolved and the patient is ready for gradual withdrawal from Neophyr treatment. The duration of the treatment should be limited to be as short as possible. The duration is variable, but typically, less than 4 days. If there is no response to the inhaled nitric oxide, consult section 4.4.

Weaning
Attempts to wean Neophyr should be made after the ventilator support is substantially decreased or after 96 hours of therapy. When the decision is made to discontinue inhaled nitric oxide therapy, the dose should be reduced to 1 ppm for 30 minutes to one hour. If there is no change in oxygenation during administration of Neophyr at 1 ppm, the FiO_2 should be increased by 10%, the Neophyr is discontinued, and the neonates monitored closely for signs of hypoxaemia. If oxygenation falls >20 %, Neophyr therapy should be resumed at 5 ppm and discontinuation of Neophyr therapy should be reconsidered after 12 to 24 hours. Infants who cannot be weaned off Neophyr by 4 days should undergo careful diagnostic work-up for other diseases.

Pulmonary hypertension associated with heart surgery
Neophyr should be used only after conservative support has been optimised. Neophyr should be administered under close monitoring of hemodynamics and oxygenation.

Newborn infants, infants and toddlers, children and adolescents, ages 0-17years
The starting dose of inhaled nitric oxide is 10 ppm(parts per million) of inhaled gas. The dose may be increased up to 20 ppm if the lower dose has not provided sufficient clinical effects. The lowest effective dose should be administered and the dose should be weaned down to 5 ppm provided that the pulmonary artery pressure and systemic arterial oxygenation remain adequate at this lower dose.

Clinical data supporting the suggested dose in the age range 12-17 years is limited.

Adults
The starting dose of inhaled nitric oxide is 20 ppm (parts per million) of inhaled gas. The dose may be increased up to 40 ppm if the lower dose has not provided sufficient clinical effect. The lowest effective dose should be administered and the dose should be weaned down to 5 ppm provided that the pulmonary artery pressure and systemic arterial oxygenation remain adequate at this lower dose.

The effects of inhaled nitric oxide are rapid, decrease in pulmonary artery pressure and improved oxygenation is seen within 5-20 minutes. In case of insufficient response the dose may be titrated after a minimum of 10 minutes.

Consideration should be given to discontinuation of treatment if no beneficial physiological effects are apparent after a 30-minute trial of therapy.

Treatment may be initiated at any time point in the perioperative course to lower pulmonary pressure. In clinical studies treatment was often initiated before separation from Cardio Pulmonary Bypass. Inhaled NO has been given for time periods up to 7 days in the perioperative setting, but common treatment times are 24 -48 hours.

Weaning
Attempts to wean Neophyr should be commenced as soon as the hemodynamics have stabilised in conjunction to weaning from ventilator and inotropic support. The withdrawal of inhaled nitric oxide therapy should be performed in a stepwise manner. The dose should be incrementally reduced to 1 ppm for 30 minutes with close observation of systemic and central pressure, and then turned off.
Weaning should be attempted at least every 12 hours when the patient is stable on a low dose of Neophyr.

Too rapid weaning from inhaled nitric oxide therapy carries the risk of a re-bound increase in pulmonary artery pressure with subsequent circulatory instability.

Additional information on special populations:

No relevant information for dosage adjustment recommendation on special populations, such as renal/hepatic impairment or geriatric, has been found. Therefore caution is recommended in these populations. The safety and efficacy of inhaled nitric oxide in premature infants less than 34 weeks of gestation has not yet been established, no recommendation or posology can be made.

Method of administration

For inhalation use.

Modalities of administration of Neophyr can modify the toxicity profile of the drug. Administration recommendations have to be followed.
Nitric oxide is normally administered by inhalation in patients via mechanical ventilation after it has been diluted with a mix of oxygen/air using a nitric oxide administration device that has been approved for clinical use as per the European Community standards (CE marked). Direct endotracheal administration without dilution is contra-indicated due to the risk of local lesion of the mucous membrane when it comes into contact with the gas.
NO must correctly mix with other gases in the ventilator circuit. It is advisable to ensure the least amount of contact time possible between the nitric oxide and the oxygen in the inspiratory circuit in order to limit the risk of the formation of toxic oxidation derivatives in the inhaled gas.
The administration system should supply a constant concentration of inhaled Neophyr, notwithstanding the ventilation equipment and ventilation modality utilised.

In order to avoid errors in the dosage, the concentration of Neophyr inhaled must be continually regulated in the inhalation branch of the circuit close to the patient, and near the tip of the endotracheal tube. The concentration of nitrogen dioxide (NO_2) and FiO_2 must also be regulated in the same place using a calibrated and EC-approved monitoring apparatus.
The concentration of NO_2 in the inhaled mix must be as low as possible. If the concentration of NO_2 exceeds 1 ppm, the dose of Neophyr and/or FiO_2 must be reduced, having ruled out any possible malfunction in the administration system.
For the safety of the patient, appropriate alarms must be configured for Neophyr (NO± 2 ppm of the prescribed dose), NO_2 (maximum 1 ppm) and FiO_2 (± 0.05: the fraction of inhaled oxygen must not vary more than 5%).
If an unexpected change in the concentration of Neophyr is produced, refer to the instruction for use of the administration device.
The pressure of the Neophyr gas cylinder must be monitored in order to allow the gas cylinder to be changed without interruptions or changes to the treatment. There must also be a reserve supply of gas cylinders to allow changes at the appropriate moment.
A back up system for the administration device must be in place, either as external device or built-in feature. The instruction for use of the device must be followed.
Neophyr therapy must be available for mechanical and manual ventilation, during transportation of the patient and during resuscitation. The doctor must have a reserve nitric oxide administration system.

Monitoring of the formation of nitrogen dioxide

Nitrogen dioxide (NO_2) forms rapidly in gaseous mixtures that contain nitric oxide and O_2.

Nitric oxide, in reaction with oxygen, will produce nitrogen dioxide (NO_2) in variable quantities depending on the NO and O_2 concentrations. NO_2 is a toxic gas that can provoke an inflammatory reaction in the respiratory tract; it is for this reason that its production must be closely monitored.

Immediately before starting the treatment on each patient, it is necessary to apply the appropriate procedures to purge the system of NO_2.

The NO2 concentration must be kept as low as possible (below0,5 ppm). If NO2 is > 0,5 ppm, the administration system must be checked according to the instruction for use of the device.

Monitoring the formation of methaemoglobin (MetHb)

Following its inhalation, the terminal compounds of nitric oxide that arrive in the systemic circulation are primarily methaemoglobin and nitrate. The nitrate is fundamentally excreted through the urinary system and the methaemoglobin is reduced by the methaemoglobin reductase.

Newborns and infants have diminished levels of MetHb reductase activity compared to adults; therefore the methaemoglobin concentrations in the blood must be monitored. The level of MetHb must be measured within 1 hour of the start of Neophyr therapy using an analyser that correctly distinguishes the fetal hemoglobin from the MetHb. If the MetHb is > 2.5%, the dose of Neophyr will have to be reduced and the necessity for the administration of reducing agents such as methylene blue will be assessed. Although considerable increases in the level of MetHb are infrequent, since the level is low during the first determination, it is advisable to repeat the MetHb measurements every 12-24 hours thereafter.

In adults undergoing heart surgery, methaemoglobin level should be measured within one hour of the initiation of Neophyr therapy. If the fraction of methaemoglobin rises to a level that potentially compromises adequate oxygen delivery, the Neophyr dose should be decreased and the administration of reducing medicinal products such as methylene blue may be considered.

Exposure limits for hospital personnel

The maximum exposure limits (average exposure) of hospital personnel to nitric oxide and nitrogen dioxide are defined in the labour legislation .
Monitoring of atmospheric levels of NO2, according to the national safety regulations, is mandatory.

Training in administration

Hospital personnel should be trained according to the instruction for use of the administration device.

4.3 Contraindications

- Newborns with known dependency to right-left blood shunt or newborns with significant left-right shunt.
- Patients with congenital or acquired deficiency of methaemoglobin reductase (MetHb reductase) or glucose 6 phosphate dehydrogenase (G6PD).
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Precautions to avoid exposures during inhaled Neophyr therapy

- Follow Standard Operating Procedures when preparing and using Neophyr.
- Install scavenging systems on ventilators to capture the patient's exhaled breath.
- Take air samples when training therapists on how to use the iNO treatment.
- Portable personal alarm devices, which warn staff if environmental levels of NO or NO_2 rise above occupational safety limits, can be provided.

Precautions to avoid accidental emptying of a gas cylinder and further actions
A spontaneous leak of nitric oxide from a gas cylinder is very rare due the exhaustive controls in the filling areas. Accidental release can happen if the cylinder falls heavily such that the valve is damaged and release occurs. To avoid that:

- Hospital staff must always secure the gas cylinder in an upright position and ensure it is firmly secured to prevent it from falling over or being knocked-over.
- The gas cylinders have to be handled with care, ensuring that they are not abruptly jolted or dropped.
- Only move gas cylinders using an appropriate type and size of vehicles and equipment for such a purpose.
- If an accidental release happens, gaseous NO leaks can be detected by a characteristic orange-brown colour and a sharp sweet and metallic smell. The recommended actions are to evacuate the room and open windows to the outside.
- In cabinet or closet stores, a fan exhausting directly to the outside should be installed to maintain a negative pressure within the cylinder storage area.
- Installation of NO and N_2 monitoring systems for continuous monitoring of NO and N_2 concentrations in enclosed NO gas cylinder storage areas and respiratory care areas to alert employees in case of an accidental release could be useful (Nitrogen gas could displace the ambient air and reduce the oxygen level in the environment).

Evaluation of the treatment response

In newborns >34 week gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, a proportion of patients that receive inhaled NO therapy do not respond to the treatment. The range of non-responders varies between 30% and 45% depending on the pre-established clinical values for favourable response. Conventional response indicators include a 20% increase in oxygenation index and/or a 20% reduction in pulmonary arterial pressure. In children, a lower response in oxygenation in new-borns with meconium aspiration syndrome has been indicated. Furthermore, the efficacy of the use of inhaled NO in patients with congenital diaphragmatic hernia has not been demonstrated in clinical trials.

If the clinical response is not considered to be adequate after 4-6 hours of Neophyr administration, the following possibilities should be considered:

- If the patient's condition continues to deteriorate or there is no improvement, the situation having been defined by pre-established criteria, the employment of a rescue system such as an ECMO will be considered, if it is indicated and possible. Persistently high levels of oxygenation index (>20) or alveolar-arterial oxygen gradient (Aao2>600) after 4 hours of iNO therapy indicate an urgent need to initiate ECMO therapy.

- In a non-response situation to the administration of Neophyr, the treatment must be suspended, but it must not be interrupted suddenly as it may provoke an increase in the pulmonary arterial pressure (PAP) and/or deterioration in blood oxygenation (PaO_2). Both situations may also occur in new-borns showing no obvious response to the Neophyr treatment. The gradual withdrawal of inhaled nitric oxide must take place with caution (See 4.2 Posology and method of administration: Withdrawal).

- In the case of patients that are to be transferred to another hospital, the supply of nitric oxide during the transportation of the patient must be guaranteed in order to avoid any deterioration in their state of health due to a sudden interruption of Neophyr treatment.

Monitoring the ventricular function

With regards to interventricular or interauricular communication, the inhalation of Neophyr causes an increase in the left-right shunt due to the vasodilator effect of the nitric oxide in the lung.
The increase in pulmonary blood flow in patients with left ventricular dysfunction can lead to cardiac insufficiency and the formation of pulmonary oedema. Careful monitoring of cardiac output, left atrial pressure, or pulmonary capillary wedge pressure is important in this situation. It is therefore recommended that before administering nitric oxide, a catheterization of the pulmonary artery or an echocardiographic examination of the central haemodynamics is carried out.

Inhaled nitric oxide should be used with caution in patients with complex heart defect, where high pressure in the pulmonary artery is of importance for maintaining circulation.
Inhaled nitric oxide should also be used with caution in patients with compromised left ventricular function and elevated baseline pulmonary capillary pressure (PCWP) as they may be at an increased risk of developing cardiac failure (e.g. pulmonary oedema).

For identifying recipients for heart transplant in dilated cardiomyopathy patients, intravenous vasodilator and inotropic therapy contribute to better ventricular compliance and prevent further elevation in left-sided filling pressures resulting from enhanced pulmonary venous return.

Monitoring haemostasis
Tests in animals have demonstrated that NO can interact with the haemostasis provoking an increase in the bleeding time. The data in adult humans is contradictory, and there has been no increase in significant bleeding complications observed in random controlled trials on new-borns.
A monitoring of the bleeding times is recommended during the course of Neophyr administration for a period of more than 24 hours in patients that suffer numerical or functional anomalies of the platelets, a deficit in the coagulation factors or that are undergoing anticoagulant treatment.

Discontinuation of therapy
The Neophyr dose should not be discontinued abruptly as it may result in an increase in pulmonary artery pressure (PAP) and/or worsening of blood oxygenation (PaO2). Deterioration in oxygenation and elevation in PAP may also occur in neonates with no apparent response to Neophyr. Weaning from inhaled nitric oxide should be performed with caution. For patients transported to other facilities for additional treatment, who need to continue with inhaled nitric oxide, arrangements should be made to ensure the continuous supply of inhaled nitric oxide during transportation. The physician should have access at the bedside to a reserve nitric oxide delivery system.

Formation of methaemoglobin
A large portion of nitric oxide for inhalation is absorbed systemically. The end medicinal products of nitric oxide that enter the systemic circulation are predominantly methaemoglobin and nitrate. The concentrations of methaemoglobin in the blood should be monitored, see section 4.2.

Formation of NO_2
NO_2 rapidly forms in gas mixtures containing nitric oxide and O2, and nitric oxide may in this way cause airway inflammation and damage. The dose of nitric oxide should be reduced if the concentration of nitrogen dioxide exceeds 0.5 ppm.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. A clinically significant interaction with other medicinal products used in the treatment of hypoxic respiratory failure cannot be excluded based on the available data.

Oxygen: In the presence of oxygen, nitric oxide oxidises rapidly forming derivatives that are toxic for the bronchiolar epithelium and the alveolo-capillar membrane. Nitrogen dioxide (NO_2) is the main compound that is formed and may cause airway inflammation and damage. There are also animal data suggesting an increased susceptibility to airway infections upon exposure to low levels of NO_2. During the treatment with nitric oxide, the concentration of NO_2 must be < 0,5 ppm in the dose interval of < 20 ppm of nitric oxide. If, at any time, the concentration of NO_2 exceeds 1 ppm, the dose of nitric oxide must be reduced immediately. See the information on monitoring NO_2 in section 4.2.

NO donors: The donor compounds of nitric oxide, including sodium nitroprusside and nitroglycerine, can have an additive effect to Neophyr with regards to the risk of developing methaemoglobinaemia.

Methaemoglobin inducers: There is a higher risk to develop methaemoglobinaemia if drugs that increase the methaemoglobin concentrations are administrated along with nitric oxide (e.g. alkyl nitrates, sulphonamides and prilocaine). As a consequence, medicinal products that increase methaemoglobin must be used with caution during inhaled nitric oxide therapy.

Prilocaine, whether administered as oral, parenteral, or topical formulations may cause methaemoglobinaemia. Care must be taken when Neophyr is given at the same time as medicinal products containing prilocaine.

Synergic effects have been reported with the administration of vasoconstrictors (almitrine, phenylephrine), prostacyclin and phosphodiesterase inhibitors, without increasing adverse effects.

Inhaled nitric oxide has been used concomitantly with tolazoline, dopamine, dobutamine, steroids, surfactants and high frequency ventilation, with no drug interactions observed.

Experimental studies suggest that nitric oxide and also nitrogen dioxide can react chemically with the surfactant and its proteins without proven clinical consequences.

The combined used with other vasodilators (e.g. sildenafil) is not extensively studied. Available data suggest additive effects on central circulation, pulmonary artery pressure and right ventricular performance. Inhaled nitric oxide combination with other vasodilators acting by the cGMP or cAMP systems should be done with caution.

Although controlled studies have not been done, food interactions have not been noticed in clinical trials in patients with prolonged ambulatory administration.

4.6 Fertility, pregnancy and lactation

Fertility
No fertility studies have been performed.

Pregnancy
The effect of the administration of Neophyr in pregnant women is unknown. Animal studies are insufficient (see section 5.3). The potential risk for humans is unknown.
Neophyr should not be used during pregnancy unless clearly necessary, such as in situations of life support.

Breast-feeding
It is not known whether Neophyr passes into human breast milk. The excretion of Neophyr in milk has not been studied in animals. Exposure to nitric oxide in humans during lactation should be avoided.

4.7 Effects on ability to drive and use machines

Infants and hospitalized patient: Not relevant.

4.8 Undesirable effects

Summary of safety profile

Abrupt discontinuation of the administration of inhaled nitric oxide may cause rebound reaction; decrease in oxygenation and increase in central pressure and subsequent decrease in systemic blood pressure. Rebound reaction is the most commonly adverse reaction in association with the clinical use of Neophyr. The rebound may be seen early as well as late during therapy.

In one clinical study (NINOS), treatment groups were similar with respect to the incidence and severity of intracranial haemorrhage, Grade IV haemorrhage, periventricular leukomalacia, cerebral infarction, seizures requiring anticonvulsant therapy, pulmonary haemorrhage, or gastrointestinal haemorrhage.

Tabulated list of adverse reactions

The adverse reactions listed are derived from CINGRI study, review of public domain scientific literature and post marketing safety surveillance (the table below shows adverse reactions that occurred in at least 5 % of patients receiving iNO in the CINRGI study). Adverse reactions are listed according to MedDRA frequency convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

System organ class	Very common	Common	Not known
Blood and lymphatic system disorders	Thrombocytopenia	-	-
Metabolism and nutrition disorders	Hypokalemia	-	-
Nervous system disorders	-		Headache*
Vascular diorders	Hypotension	-	Pulmonary artery pressure increased** Hypotension**
Respiratory, thoracic and mediastinal disorders	Atelectasis	-	-
Hepatobiliary disorders	Hyperbilirubinemia		
Investigations			Methaemo globin increased, Hypoxemia**

* Post-Marketing Safety Surveillance (PMSS) data, symptom experienced by personnel associated to accidental environmental exposure
**PMSS data, effects associated with acute withdrawal of the medicinal product, and dose errors associated with the delivery system. Rapid rebound reactions such as intensified pulmonary vasoconstriction after sudden withdrawal of inhaled nitric oxide therapy has been described, precipitating cardiovascular collapse.

Description of selected adverse reactions
Inhaled nitric oxide therapy may cause an increase in methaemoglobin.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517; Website: www.hpra.ie; e-mail: medsafety@hpra.ie

4.9 Overdose

Overdose with Neophyr will be manifest by elevations in methaemoglobin and NO_2. Elevated NO_2 may cause acute lung injury. Elevations in methaemoglobinaemia reduce the oxygen delivery capacity of the circulation. In clinical studies, NO_2 levels > 3 ppm or methaemoglobin levels > 7 % were treated by reducing the dose of, or discontinuing, iNO.

Methaemoglobinaemia that does not resolve after reduction or discontinuation of therapy can be treated with intravenous vitamin C, intravenous methylene blue, or blood transfusion, based upon the clinical situation.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other respiratory system products, ATC code R07AX01.

Nitric oxide is a compound produced by many cells of the body. It relaxes vascular smooth muscle by binding to the haeme moiety of cytosolic guanylate cyclase, activating guanylate cyclase and increasing intracellular levels of cyclic guanosine 3',5'-monophosphate, which then leads to vasodilation. When inhaled, nitric oxide produces selective pulmonary vasodilation. iNO appears to increase the partial pressure of arterial oxygen (PaO2) by dilating pulmonary vessels in better ventilated areas of the lung, redistributing pulmonary blood flow away from lung regions with low ventilation/perfusion (V/Q) ratios toward regions with normal ratios.

Persistent pulmonary hypertension of the newborn (PPHN) occurs as a primary developmental defect or as a condition secondary to other diseases such as meconium aspiration syndrome (MAS), pneumonia, sepsis, hyaline membrane disease, congenital diaphragmatic hernia (CDH), and pulmonary hypoplasia. In these states, pulmonary vascular resistance (PVR) is high, which results in hypoxemia secondary to right-to-left shunting of blood through the patent ductus arteriosus and foramen ovale. In neonates with PPHN, iNO can improve oxygenation (as indicated by significant increases in PaO2).

The efficacy of iNO has been investigated in term and near-term newborns with hypoxic respiratory failure resulting from a variety of etiologies.

In the NINOS trial, 235 neonates with hypoxic respiratory failure were randomised to receive 100 % O2 with (n=114) or without (n=121) nitric oxide most with an initial concentration of 20 ppm with weaning as possible to lower doses with a median duration of exposure of 40 hours. The objective of this double-blind, randomised, placebo controlled trial was to determine whether inhaled nitric oxide would reduce the occurrence of death and/or initiation of extracorporeal membrane oxygenation (ECMO). Neonates with less than a full response at 20 ppm were evaluated for a response to 80 ppm nitric oxide or control gas. The combined incidence of death and/or initiation of ECMO (the prospectively defined primary endpoint) showed a significant advantage for the nitric oxide treated group (46 % vs. 64 %, p=0.006). Data further suggested a lack of additional benefit for the higher dose of nitric oxide. The adverse events collected occurred at similar incidence rates in both groups.
Follow-up exams at 18-24 months of age were similar between the two groups with respect to mental, motor, audiologic, and neurologic evaluations.

In the CINRGI trial, 186 term- and near-term neonates with hypoxic respiratory failure were randomised to receive either iNO (n=97) or nitrogen gas (placebo; n=89) with an initial dose of 20 ppm weaning to 5 ppm in 4 to 24 hours with median duration of exposure of 44 hours. The prospectively defined primary endpoint was the receipt of ECMO. Significantly fewer neonates in the iNO group required ECMO compared to the control group (31 % vs 57 %, p<0.001). The iNO group had significantly improved oxygenation as measured by PaO2, OI, and alveolar-arterial gradient (p<0.001 for all parameters). Of the 97 patients treated with , 2(2 %) were withdrawn from study drug due to methaemoglobin levels >4 %. The frequency and number of adverse events were similar in the two study groups.

In patients undergoing heart surgery, an increase in pulmonary artery pressure due to pulmonary vasoconstriction is frequently seen. Inhaled nitric oxide has been shown to selectively reduce pulmonary vascular resistance and reduce the increased pulmonary artery pressure. This may increase the right ventricular ejection fraction. These effects in turn lead to improved blood circulation and oxygenation in the pulmonary circulation.

In the INOT27 trial, 795 preterm infants (GA<29 weeks) with hypoxic respiratory failure were randomised to receive either iNO (n=395) in a dose of 5 ppm or nitrogen (placebo n=400), beginning within the first 24 hours of life and treated for at least 7 days, up to 21 days. The primary outcome, of the combined efficacy endpoints of death or BPD at 36 weeks GA, was not significantly different between groups, even with adjustment for gestational age as a covariate (p = 0.40), or with birth weight as a covariate (p = 0.41). The overall occurrence of intraventricular haemorrhage was 114 (28.9 %) among the iNO treated as compared to 91 (22.9 %) among the control neonates. The overall number of death at week 36 was slightly higher in the iNO group; 53/395 (13.4 %) as compared to control 42/397 (10.6 %). The INOT25 trial, studying the effects of iNO in hypoxic preterm neonates, did not show improvement in alive without BDP. No difference in the incidence of IVH or death was however observed in this study. The BALLR1 study, also evaluating the effects of iNO in preterm neonates, but initiating iNO at 7 days and in a dose of 20 ppm, found a significant increase in neonates alive without BPD at gestational week 36, 121 (45 % vs 95 (35.4 %) p<0.028. No signs of any increase adverse effects was noted in this study.

Nitric oxide chemically reacts with oxygen to form nitrogen dioxide.

Nitric oxide has an unpaired electron, which makes the molecule reactive. In biological tissue, nitric oxide may form peroxynitrite with superoxide (O2 -), an unstable compound which may cause tissue damage through further redox reactions. In addition, nitric oxide has affinity to metalloproteins and may also react with SH-groups in protein forming nitrosyl compounds. The clinical significance of the chemical reactivity of nitric oxide in tissue is unknown. Studies show that nitric oxide exhibits pulmonary pharmacodynamic effects at intra-airway concentrations as low as 1 ppm.

The European Medicines Agency has waived the obligation to submit the results of studies with iNO in all subsets of the paediatric population in persistent pulmonary hypertension and other pulmonary heart disease (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of nitric oxide has been studied in adults. Nitric oxide is absorbed systemically after inhalation. Most of it traverses the pulmonary capillary bed where it combines with haemoglobin that is 60 % to 100 % oxygen-saturated. At this level of oxygen saturation, nitric oxide combines predominantly with oxyhaemoglobin to produce methaemoglobin and nitrate. At low oxygen saturation, nitric oxide can combine with deoxyhaemoglobin to transiently form nitrosylhaemoglobin, which is converted to nitrogen oxides and methaemoglobin upon exposure to oxygen. Within the pulmonary system, nitric oxide can combine with oxygen and water to produce nitrogen dioxide and nitrite, respectively, which interact with oxyhaemoglobin to produce methaemoglobin and nitrate.
Thus, the end products of nitric oxide that enter the systemic circulation are predominantly methaemoglobin and nitrate.

Methaemoglobin disposition has been investigated as a function of time and nitric oxide exposure concentration in neonates with respiratory failure. Methaemoglobin concentrations increase during the first 8 hours of nitric oxide exposure. The mean methaemoglobin levels remained below 1 % in the placebo group and in the 5 ppm and 20 ppm iNO groups, but reached approximately 5 % in the 80 ppm iNO group. Methaemoglobin levels > 7 % were attained only in patients receiving 80 ppm, where they comprised 35 % of the group. The average time to reach peak methaemoglobin was 10 ± 9 (SD) hours (median, 8 hours) in these 13 patients; but one patient did not exceed 7 % until 40 hours.

Nitrate has been identified as the predominant nitric oxide metabolite excreted in the urine, accounting for > 70 % of the nitric oxide dose inhaled. Nitrate is cleared from the plasma by the kidney at rates approaching the rate of glomerular filtration.

5.3 Preclinical safety data

Effects seen in single and repeat dose-toxicity studies in rodents were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. Toxicity is related to anoxia resulting from elevated methaemoglobin levels.

No reproductive and developmental toxicity studies have been performed.

A battery of genotoxicity tests has demonstrated mutagenic potential of nitric oxide in some in vitro test systems and no clastogenic effect in the in vivo system. This is possibly related to the formation of mutagenic nitrosamines, DNA alterations or impairment of DNA repair mechanisms. A low incidence in uterine adenocarcinomas in rats following daily exposure to the recommended human dose for two years was tentatively considered treatment related. The significance of these findings for clinical use in neonates and the potential for effects on the germ cells are unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Nitrogen

6.2 Incompatibilities

See section 4.5 for the incompatibilities with other medicinal products.

The administration system must be approved for the use with NO, see section 6.6.

6.3 Shelf life

3 years

6.4 Special precautions for storage

All regulations concerning handling of pressurised cylinders must be followed.
Storage is supervised by the specialists at the hospital. Cylinders are to be stored in well-ventilated rooms or in ventilated sheds where they are protected from rain and direct sunlight.

The cylinders must be stored at a temperature between -10 and +50°C.

Protect the cylinders from shocks, falls, oxidising and flammable materials, moisture, sources of heat or ignition.

Storage in the pharmacy department
The gas cylinders should be kept in a place designated exclusively for medicinal gas storage that is well ventilated, clean and under lock and key. This place should house a separate, special facility for the storage of nitric oxide gas cylinders.

Storage in medical department
The cylinder should be placed in an area with appropriate equipment to ensure that the cylinder is held vertically.

Transport of gas cylinders
The gas cylinders should be transported with appropriate material in order to protect them from the risk of shocks and falls.During inter- or within-hospital transfers of patients treated with Neophyr, the gas cylinders should be securely stowed away in order to hold the gas cylinders vertically and to avoid the risk of falls or untimely modifying output. Particular attention should be also turned to the fastening of the pressure regulator so as to avoid the risk of accidental failures.

Do not use Neophyr after the expiry date which is stated on the gas cylinder label. The expiry date refers to the last day of that month.

6.5 Nature and contents of container

Gas cylinders with a capacity of 10l.
A 10-liter gas cylinder filled to 150 bar contains about 1.77 kg of gas.
Aluminum alloy cylinders have a white painted body and a turquoise-painted shoulder.
They are equipped with a stainless steel residual pressure valve with a specific ISO 5145 (2004) type outlet connector.

6.6 Special precautions for disposal and other handling

All equipment used, including connectors, tubing and circuits, must be a medical device whose intended use is the administration of NO.

To avoid any incidents, refer to the instruction for use of the device.

At least the following instructions must be strictly adhered to:

- check that the equipment is in working order before use.
- firmly secure the cylinders using chains or hooks in the rack to avoid any accidental falls
- never open a valve abruptly
- do not handle a cylinder on which the valve is not protected by a guard

- use a specific ISO 5145 (2004) connector: n°29 specific NO/N2 (100 ppm< NO < 1000 ppm) W30x2 15,2-20,8 DR

- do not attempt to repair a defective valve.
- evacuate exhaled gases outside (avoiding areas in which they may accumulate). Before use, it should be ensured that the room has the appropriate ventilation system for evacuating gases in the event of an accident or accidental leaks.
- If an accidental release happens, gaseous NO leaks can be detected by a characteristic orange-brown colour and a sharp sweet and metallic smell. The recommended actions are to evacuate the room and open windows to the outside
- personnel exposure limits (see section 4.2: Dosage and route of administration)

Instruction for cylinder disposal:
When the cylinder is empty, do not dispose of it. Empty cylinders will be collected by the supplier.

7 MARKETING AUTHORISATION HOLDER

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20900 Monza
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8 MARKETING AUTHORISATION NUMBER

PA1848/001/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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